V. APPENDICES

Appendix 1
Detailed Cost Estimate

Principal Investigator ***(last, first, middle)***

DETAILED BUDGET FOR INITIAL BUDGET PERIOD			**FROM**		**THROUGH**
PERSONNEL (APPLICANT ORGANIZATION ONLY)		**TYPE APPT. (MONTHS)**	**ANNUAL BASE SALARY**	**%EFFORT ON PROJECT**	**DOLLAR AMOUNT REQUESTED (OMIT CENTS)**		
NAME	**ROLE ON PROJECT**				**SALARY REQUESTED**	**FRINGE BENEFITS**	**TOTALS**
	Principal Investigator						
PERSONNEL DIRECT COSTS SUBTOTALS →→→→→→→→→→→							**$**
CONSULTANT COST							
EQUIPMENT (ITEMIZE)							
SUPPLIES (ITEMIZE BY CATEGORY)							
TRAVEL							
RESEARCH-RELATED PATIENT COST							
OTHER EXPENSES (ITEMIZE BY CATEGORY)							
SUBTOTAL OTHER DIRECT COSTS FOR INITIAL BUDGET PERIOD →→→→→→→→→→→→→→							**$**
TOTAL PERSONNEL & OTHER DIRECT COSTS FOR INITIAL BUDGET PERIOD							**$**
TOTAL INDIRECT COSTS FOR INITIAL BUDGET PERIOD							**$**
TOTAL COSTS FOR INITIAL BUDGET PERIOD							**$**

Principal Investigator ***(last, first, middle)***

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT					
BUDGET CATEGORY TOTALS*	INITIAL BUDGET PERIOD (FROM FORM PAGE 1)	ADDITIONAL YEARS OF SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL					
FRINGE BENEFITS					
CONSULTANT COST					
EQUIPMENT					
SUPPLIES					
TRAVEL					
RESEARCH-RELATED PATIENT COST					
OTHER EXPENSES					
SUBTOTAL DIRECT COST					
TOTAL DIRECT COST					
TOTAL INDIRECT COST					
TOTAL DIRECT COST FOR ENTIRE PROPOSED PERIOD OF SUPPORT				$	
TOTAL INDIRECT COST FOR ENTIRE PROPOSED PERIOD OF SUPPORT				$	
TOTAL COST FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT THIS AMOUNT MUST AGREE WITH THAT ENTERED ON THE COVER SHEET BOOKLET, ITEM #22				$	

*** Itemize all budget categories for additional years on *Justification* page which follows**

JUSTIFICATION: FOLLOW THE BUDGET JUSTIFICATION INSTRUCTIONS EXACTLY. USE CONTINUATION PAGES AS NEEDED.

Appendix 2
Biographical Sketches

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel listed on the budget page for the initial budget period

NAME	POSITION TITLE

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY.
DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY.
DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Appendix 3
Regulatory Compliance Checklist/Form

This form MUST be completed and sent in when appendices are requested.

Human Subjects: ***Please read Appendix 5 before completing. Mark all that apply.***

- ○ Females
- ○ Males
- ○ Minor (under 18)
- ○ Minorities
- ○ Military, Active Duty
- ○ Military, Reserve
- ○ National Guard
- ○ Foreign
- ○ Inpatient
- ○ Outpatient
- ○ Clinical Trials
- ○ Other (specify): _____

Human Anatomical Substances: ***Please read Appendix 5 before completing.***

In the proposed work, will human anatomical substances be used?

○ Yes ○ No

If yes, which anatomical substance(s) will be used (mark all that apply):

- ○ Blood
- ○ Saliva
- ○ Tissue
- ○ Established Cell Lines
- ○ Cells
- ○ Primary Cell Lines
- ○ DNA
- ○ Other (specify): _____
- ○ Urine

Can the anatomical substance(s) indicated above be traced to a specific donor?

○ Yes ○ No

CONTINUED ON REVERSE

Animal Subjects: ***Please read Appendix 6 before completing.***

In the proposed work, will animals be used?

○ Yes ○ No

In the proposed work, will animals be used by a subcontractor?

○ Yes ○ No

If yes to either of the above questions, which animal subjects will be used (mark all that apply):

○ Primates
○ Frogs
○ Rabbits
○ Hamsters
○ Horses
○ Cats
○ Chickens
○ Fish
○ Ferrets
○ Sheep
○ Dogs
○ Pigeons
○ Rodents
○ Guinea pigs
○ Goats
○ Other (specify): _____

Safety Provisions: ***Please read Appendix 7 before completing. Mark all that apply.***

○ Good Laboratory Practices (GLP)
○ Recombinant DNA
○ Investigational Drugs
○ Radioactive Materials
○ Genetic Materials
○ Biologicals/Toxins
○ Hazardous Materials
○ Other (specify): _____

Appendix 4
Certificate of Environmental Compliance

The offeror currently ____ IS ___ IS NOT (check appropriate category) in compliance with applicable national, state, and local environmental laws and regulations. (If not in compliance, attach details and evidence of approved mitigation measures.)

The offeror has examined the activities encompassed within the proposed action entitled "_____

_____"

(enter title and/or Solicitation number and Principal Investigator's name), for compliance with environmental laws and regulations. The offeror states that the conduct of the proposed action

1. WILL NOT violate any applicable national, state, or local environmental law or regulation.

2. WILL NOT have a significant impact on the environment.

The offeror agrees that if the work required under the proposed action at any time results in a significant impact on the environment or a violation of any applicable environmental law or regulation, the offeror will immediately take appropriate action, to include notifying and/or coordinating with the appropriate regulatory agencies as required by law and notifying the Contracting Officer.

_____ _____

Name of Official Responsible for Environmental Compliance

Signature

_____ _____

Title

Date

_____

Name of Organization

Appendix 5
Research Involving Human Subjects and/or Human Anatomical Substances

(includes DNA, cells, tissues, blood, etc.)

The intention of this appendix is to provide clear, concise information that will enable each PI to prepare documentation for human use and regulatory compliance review by the U.S. Army Medical Research and Materiel Command (USAMRMC), Deputy Chief of Staff for Regulatory Compliance and Quality (RCQ), Human Use Review and Regulatory Affairs (HURRAD). A synopsis of the guidance contained in the code of Federal Regulations, DOD Directives, and Army Regulations is provided at the end of this appendix (page A-27). If only anatomical substances will be used, see Section A (below) for guidance. If human subjects or data about human subjects (inclusive of database studies) will be used, see pages A-16 - A-29 (Section B). **These requirements may differ from those of other funding agencies.**

Section A
Guidance for Use of Human Anatomical Substances

1. **GENERAL:** It is important to note clearly what type of human anatomical substances will be used, and how the substances will be used, in the research study. This section provides guidance for use of human blood, tissue, urine, saliva, cells, established cell lines, primary cell lines, DNA, and other associated substances.

2. SPECIFIC GUIDANCE:

a. Human Blood, Tissue, Urine, Saliva, DNA, etc.

1. If the blood, tissue, urine, saliva, DNA, or other anatomical substance used in the study *contains no personal identifiers and was not obtained for the purpose of this research (existing)*, the study is considered to be exempt from human use regulations. The Optional Form 310 should be completed and signed by the Chair of the local Institutional Review Board, indicating the study is exempt. It should be noted in the comments block that the study will use existing blood, tissue, urine, saliva, DNA, etc. with no personal identifiers linking the substance to the donor. This will be the sole document required for submission of the Human Use Appendix for this type of research.

2. If the blood, tissue, urine, saliva, DNA, or other anatomical substance used in the study ***does contain*** *personal identifiers or was obtained specifically for the purpose of this research*, the study is considered to be minimal risk. An informed consent document written according to instructions in Section B must be prepared (See pages A-20 - A-24).

The Optional Form 310 must be completed and signed by the Chair of the local Institutional Review Board, indicating the study is minimal risk. The consent form and completed Optional Form 310 will be the documents required for submission of the Human Use Appendix for this type of research.

b. Cells, Established Cell Lines, Primary Cell Lines, etc.

It should be clearly indicated how these anatomical substances were obtained. If the cells were purchased, it should be indicated from whom the purchase was made (or will be made). The use of these substances is considered exempt from human use regulations. The Optional Form 310 should be completed and signed by the Chair of the local Institutional Review Board, indicating the study is exempt. It should be noted in the comments block how the substances were obtained, purchased, etc. This will be the sole document required for submission of the Human Use Appendix for this type of research.

3. OPTIONAL FORM 310: A copy of an Optional Form 310 is included on page A-29. This form is also available at the following World Wide Web site: **http://mrmc-rad6.army.mil/documents.html**

4. QUESTIONS: Questions regarding the use of human anatomical substances should be directed to fax number (301)619-7803.

5. SUGGESTIONS: Suggestions for improving or clarifying this section should also be directed to fax number (301)619-7803.

Section B
Guidance for Use of Human Subjects

1. GENERAL: Each protocol submission should include a protocol, a consent form, and a completed Optional Form 310. If applicable, a copy of the advertisements, questionnaires, case report forms, IND information, and other related information should be provided with the Human Use Appendix. **All revisions to the protocol, consent form, advertisements, questionnaires, and other related study documentation must be reviewed and approved by the HURRA prior to implementation.**

2. SPECIFIC GUIDANCE:

a. Protocol Review Checklist: This checklist is designed to assist the applicant in preparing a protocol. Please disregard items that to not apply.

- PROJECT TITLE. The consent form title must match that of the project.
- PHASE. For Food, Drug, and Cosmetic Act regulated medical products, designate as a Phase I, II, III, or IV protocol.
- PRINCIPAL INVESTIGATOR. The complete name, address, and phone number of the PI must be listed at the top.
- LOCATION OF STUDY. List all centers, clinics, or laboratories where the study is to be carried out. The complete addresses and site investigator(s) should be listed.
- TIME REQUIRED TO COMPLETE. The month/year of expected start and completion dates must be listed.
- PLAN. Outline exactly the proposed methodology in enough detail to show a clear course of action. Technological reliability and validity of procedures should be indicated, and chronological order should be followed. Minimum guidance for the plan includes:
  - Selection of subjects
  - Number of subjects
  - Age range
  - Sex
  - Inclusion criteria/diagnostic criteria for entry/exclusion criteria (If women and/or minorities will be excluded, a justification as to why must be included.)
  - Evaluations prior to entry
  - Source of subjects
  - Subject identification (Describe code system to be used.)

- Subject assignment
- Risks to the subject
- Precautions to be taken to minimize/eliminate risks
- Specific medical or nursing care that will be needed
- Description of project medication(s) or device(s) (If investigational, provide the IND number and sponsor.)
- Complete names and composition of all medication(s)/device(s)/placebo(s)
- Source of medication(s)/device(s)/placebo(s)
- Place where study medication(s) will be stored
- Dose range/dose schedule/administration
- Washout period (The washout or pre-drug period must be carefully noted.)
- Duration of drug or device treatment
- Accompanying medications (Those allowed/disqualified)
- Antidotes to be available
- Copy of the medication/device label
- Evaluations made during/following project

NOTE: IT IS VERY IMPORTANT TO STATE DETAILS PERTAINING TO THE FOLLOWING IN THE PROTOCOL.

1. Specimens to be collected
2. Schedule and amounts
3. Evaluations to be made on specimens
4. Storage (Include storage locations and whether special conditions are required.)
5. Labeling and disposition
6. Clinical assessments (Include how adverse effects are to be recorded.)
7. Vital signs
8. Follow-up procedures
9. Disposition of data (Where stored and for how long? Note: Records for IND studies must be kept until two years after an NDA/license for the investigational drug is approved/issued or for two years after the IND is withdrawn.)
10. Biostatistical reviews
11. Departure from protocol for individual subjects (When allowed, who will be notified; include HURRA.)
12. Modification of protocol (Describe the procedure to be followed if the protocol is modified. Include HURRA.)
13. Disposition of unused drug
14. Use of information/publications arising from study
15. Personnel to conduct project (Names, positions, and phone numbers. Include the medical monitor. Attach a short biographical sketch. Include a resume of education, research training, and list of publications for each person.)

THE FOLLOWING SIGNATURES ARE REQUIRED FOR ALL PROTOCOLS:

1. Signature of PI, date, with the accompanying statement--
   "I have read the foregoing protocol and agree to conduct the study as outlined herein."
2. Signature of appropriate approving official and date.

ADDITIONAL CONSIDERATIONS:

- ✔ A **medical monitor** must be assigned to human subjects research involving greater than minimal risk. The name and the curriculum vitae of the medical monitor must be provided. This individual should be a qualified physician, other than the PI, who is not associated with the protocol, is able to provide medical care to research subjects for conditions that may arise during the conduct of the study, and will monitor the subjects during the conduct of the study. (For multi-center studies involving greater than minimal risk, a medical monitor must be assigned to each site.)

- ✔ If **HIV screening** is to be done, the consent form must further state that results will be provided to the subject and that medical referrals and follow-up will be available to subjects found to be HIV positive.

- ✔ A **science review** should be documented.

- ✔ The **method of determining pregnancy** status in women of childbearing potential must be specified, if applicable. Also, the time that will elapse between the pregnancy test and exposure to test procedures or medical products must be documented. Serum pregnancy tests are required for all clinical medical product studies. For IND studies, serum pregnancy testing is required within 48 hours prior to the start of the study.

- ✔ For **IND studies** that include females of childbearing age, any risks to the developing fetus should be outlined in the consent form.

- ✔ A letter from the Radiation Protection Officer at the study site approving the use of **radio-labeled products** must be included, if applicable.

- ✔ If there will be **collaborators** in the study, all letters of collaboration must be included.

- ✔ If the project is conducted in a **foreign country**, a letter of approval from the Ministry/ Minister of Health or equivalent approving official from the foreign country must be included.

- ✔ Also, a sample, if applicable, of any test to ensure comprehension by the subjects of the proposed study must be included.

✔ If a foreign study, the **foreign version of the consent form** must be included. In addition, the following statement and information is required on the English-language version of the translated consent form: "I certify that this is an accurate and true translation." The translator's signature, name, address, phone number, and fax number should also be included.

✔ If the study involves a **contagious disease**, any other studies going on in the isolation ward at the same time should be discouraged.

☛**10 USC 980. An intent to benefit subjects who cannot give their own consent (minors, unconscious) must be shown. This intent must be clearly stated in the protocol and consent form.**

✔ If **military subjects** are involved in a study and blood is to be drawn, they may be paid only for their blood donation and only up to $50.00 per draw unless the study participation will be conducted during off-duty hours. This must be clearly stipulated. If payment will be provided to subjects in the study, it should be clearly stated who (military vs. civilian, if applicable) will be paid what amount, and when and how that payment will be made.

✔ All **payments to the subject** for their participation in the research must be made clear in both the protocol and the consent form. The pro-rated amount should subjects be withdrawn during the study must be indicated. It should also be indicated how and when payment will be made.

✔ The collection of **minority group data** is suggested for inclusion in the study, e.g., American Indian or Alaska Native, Asian or Pacific Islander, Black (not Hispanic Origin), Hispanic, White (not Hispanic Origin), for future data analysis, in accordance with Public Law 103-160 and the Department of Health and Human Services and the Food and Drug Administration guidelines.

b. Elements of Informed Consent: Informed consent is more than a document, it is a continual process. In preparing your informed consent document, please include all of the elements below that apply. 32 CFR 219 and 45 CFR 46 provide additional guidance for elements that are not listed below. If a multi-center study is proposed, the investigator must submit one consent form from each site for review and approval. That consent form must be used at each study site. Consent forms should be written in 8th grade reading level language. Use short, clear, simple, declarative sentences. Use non-medical language that is easily understood by the subject. *Elements listed in italics must be included in all consent forms.*

1. *Title of the study and complete address.*

2. ***Name** of the PI, and associate(s) if applicable, conducting the study.*

3. *A statement that the study **involves research.***

4. ***Purpose of the research.***

5. Provide a **translation** of the consent form for subjects being enrolled in the study who do not comprehend English. The following statement and information is required on the English language version of the translated consent form: **"I certify that this is an accurate and true translation."** (The translator's signature, name, address, phone number, and fax number should also be included.)

6. *Include a statement clearly indicating the expected **duration** of the subject's participation (the number of hours, days, etc.).*

7. *Describe all **procedures** to be followed and identify any procedures that are experimental. These procedures should agree with the protocol.*

8. *Briefly explain the **study design** relative to what will be done to the subject in 8th grade reading level language. Use short, clear, simple declaritive sentences. Use non-medical language that is easily understood by the subject.*

9. If a **placebo** is used, its contents should be described, in lay terms.

10. Specify what is **required of the subject** (hospital visits, blood donation, etc.).

11. If **blood** is to be drawn (including serum pregnancy tests), the amount(s) to be drawn should be expressed in lay terms (for example, 2 teaspoons).

12. The subject should be advised that the IND/IDE is being used in this study. Clearly indicate that its use is investigational for the purposes of this research.

13. Include **risks or discomforts** to the subject. (This includes pregnancy and possible risks to the fetus.)

14. Will **pregnant women** be excluded and/or withdrawn from the study?

15. ***Risks** should include risks unique to the study; estimate their severity and likelihood; and/or compare these risks with risks the subject might encounter in the course of his/her daily activities. If similar research has been conducted in the past, describe the incidence of adverse effects or injuries occurring in previous subjects.*

16. ***Benefits*** *of participation in the study should be listed.*

17. ***Alternative procedures*** *should be disclosed.*

18. **Payment** for study participation should be disclosed (see page A-20).

19. ***Confidentiality*** *of records identifying the subject must be described.*

20. *The following statement is MANDATORY for studies utilizing* ***civilians:*** *"Representatives from the U.S. Army Medical Research and Materiel Command (and, where applicable, the Food and Drug Administration, and the U.S. Army Medical Department Center and School) may inspect the records of the research in their duty to protect human subjects in research."*

21. *The following statement is MANDATORY for studies utilizing* ***military personnel****: "All data and medical information obtained about you as an individual will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or Command authorities. Representatives of the U.S. Army Medical Research and Materiel Command [and the Food and Drug Administration] may inspect the records of the research."*

22. ***Medical care*** *clause: "The Department of Defense is funding this research project. Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the PI before you enroll in this study."*

23. ***Points of Contact:***
    a. *Answers to questions* ***about the research*** *study and in the event of a research-related* ***injury*** *to the subject should be provided by the investigator.*
    b. *Answers to questions about research subjects'* ***rights*** *should be provided by the local IRB or legal office.*

24. *A statement should be included that participation is* ***voluntary****, that refusal to participate will involve* ***no penalty or loss of benefits*** *to which the subject is otherwise entitled, and that the subject may* ***discontinue participation*** *at any time without penalty or loss of benefits to which the subject is otherwise entitled.*

25. *The **Signature Block** should include the date, signature, typed/printed name, and permanent address of subject, and signature and typed/printed name of witness. If using Department of the Army active duty soldiers, contact Human Use Review and Regulatory Affairs for the appropriate Department of the Army form.*

26. *The subject and witness should **initial** and date all but the last page.*

27. If **blood, tissue, or body product samples** will be drawn in the study for possible future use in another protocol, the following statement **must be included**: "I understand that there is a possibility that the [blood, tissue, body fluids--specify what type] that I am providing under this study may also be used in other research studies and could potentially have some commercial applicability."

    If, indeed, it is anticipated that the samples donated by the volunteer will be used in other studies, an **additional donation form** must be prepared for signature by the volunteer that states "I voluntarily and freely donate any and all [blood, tissue, body fluids--specify what type] to the [name of the institution] and the U.S. Government and hereby relinquish all right, title, and interest to said items." The title of the study should be inserted at the top of the form.

28. *It should be clearly indicated whether the subject will be asked to pay any **Costs** associated with this study. If so, list what tests, etc. for which the subject will be responsible for paying. Also, if the cost of the study drug will be charged to the subject, it should be indicated.*

29. If **pregnant women** will be excluded, the following statement (or equivalent) must be included: "In order to participate in this study, you should have avoided becoming pregnant from the first day of your most recent menses. You should avoid becoming pregnant for at least [time period in days, weeks, or months] after [study end date, receipt of drug, etc.]. Pregnancy within [time period in days, weeks, or months] after [study end date, receipt of drug, etc.] may create a potential risk to the unborn baby. To avoid becoming pregnant, you should either abstain from sexual relations or practice a method of birth control. The only ways to completely avoid risk to the unborn baby are (1) to not become pregnant or (2) do not enter this study. Adverse effects might affect a developing fetus. Further, they might result in unknown risks of deformities or death to the unborn baby. A negative pregnancy test does not absolutely prove that you are not pregnant. Regardless of the results of the pregnancy test that you were administered as part of the screening for this study, you should not participate if you think there is a possibility that you might be pregnant." Also, a statement should be included which directs the volunteer to notify the PI if she becomes pregnant. Women should be notified if they will be withdrawn from the study should they become pregnant.

30. For all studies involving more than minimal risk, the following statement must be included in the consent form: "By enrolling in this study, you should understand that the United States Army Medical Research and Materiel Command (USAMRMC) will collect certain information about you, including your name, address, social security number, study name, and dates. The purpose is, first, to readily answer an individual's questions about their participation in research sponsored by the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned of risks and to provide new information as it becomes available. The information will be retained in this database for a minimum of 75 years."

31. Each page should be dated using the date that the document was edited (ex: Ver 1.0/ March 1, 1997).

c. Optional Form 310 (OF 310): Each institution must have an assurance of compliance with human use regulations. If an institution has a Multiple Project Assurance (MPA) on file with the Department of Health and Human Services (DHHS) Office for Protection from Research Risks, that assurance number should be documented on the OF 310 (page A-29), Protection of Human Subjects Assurance/Certification/Declaration which replaced DHHS Form 596. If the institution does not have an MPA, an assurance application should be completed and sent with the protocol. A Department of Defense Assurance will be issued for the research project. There are three different assurance applications: (1) for institutions that have an IRB but no MPA; (2) for overseas institutions; and (3) for institutions that must use another institution's IRB. These assurance applications and the OF 310 can be downloaded from the World Wide Web site: **http://mrmc-rad6.army.mil/documents.html**

The OF 310 should be completed and signed by the Chairperson of the IRB. If another agent signs this document, verification of authority should be included in the remarks column (individual's signature authority). The **OF 310 must** include the level of risk that the project poses to the subject. These risk levels are: exempt, minimal risk, and greater than minimal risk. The HURRA reserves the right to determine whether the risk level is in compliance with all applicable regulations. If the study has been determined to be exempt, the PI must clearly state the information requested under "Specific Guidance" (pages A-15 - A-16). ***Risk Level Determination (exempt, minimal, or greater than minimal risk) should be indicated in the comments section.***

d. Advertisement: If subjects will be recruited through an advertisement, newspaper article, or similar process, a copy of the IRB-approved advertisement must be provided. IRB review of advertisements is necessary to ensure the information is not misleading to the subjects participating in IND studies. The FDA has established guidelines on advertisements for subjects. General guidance includes: name and address of PI, summary of research purpose, brief eligibility criteria, truthful list of benefits, and the person to contact for further information.

e. Questionnaires, Case Report Forms, Study Instruments, etc.: Include copies of all other applicable study-related documentation: questionnaires, case report forms, data sheets, etc.

3. ANSWERS TO FREQUENTLY ASKED QUESTIONS:

a. ***What is the Medical Care Provision?*** - Civilians must be provided medical care, free of charge, if they are injured as a direct result of their participation while enrolled in research funded by the USAMRMC. The proposed recipient must agree to provide this medical care. This is a requirement for all protocols funded by the USAMRMC, regardless of risk level. The consent form guidance (detailed on pages A-20 - A-24) provides a recommended statement to inform research subjects of this requirement. If the proposed recipient wishes to use similar wording, that wording will be reviewed upon submission. However, the proposed recipient's statement must concur with the USAMRMC policy of providing medical care, free of charge. Research will not be approved if the proposed contractor does not have a mechanism in place to provide this care. The mechanism used should be clearly stated in the consent form. Four possible mechanisms are as follows:

1. The proposed recipient may absorb such costs into the institution's operating budget.

2. The proposed recipient's liability insurance, if available, may be sufficient to cover any medical care costs. The proposed recipient's business office and/or legal advisor must ensure that there is adequate coverage under this liability insurance.

3. The proposed recipient could negotiate an additional amount of funds, if available, into the award that will cover such medical care cost (such as liability insurance). This can only be negotiated with the U.S. Army Medical Research Acquisition Activity (the contracting organization).

4. Third-party payers may be billed for such medical expenses. If this method is used, the subject must be informed, in the consent document, that his/her insurance company will be billed. The proposed recipient must also state, and agree to, an assurance that any payments not covered by the third-party insurance will be paid by the proposed recipient.

b. ***What is the Volunteer Registry Database?*** - A confidential database has been created to enable the USAMRMC to fulfill its "duty to warn." The information contained in the database is cited on USAMRMC Form 60-R (Volunteer Registry Data Sheet). This data sheet will be provided to the PI, upon approval of the use of human subjects. This form may be copied by the PI. Data collection is required for all studies considered greater than minimal risk. All information obtained in this database is protected under The Privacy Act of 1974. Information about the study itself could be released to a requestor. However, personal identifying information (name, address, date of birth, social security number, etc.)

may not, and will not, be released unless the subject (or legal guardian) provides written approval of such disclosure. Each subject on whom data are collected, upon written request to HURRA, RCQ, USAMRMC, may have access to their record, and only their record, contained in the database. The data sheets must be completed for each subject enrolled in the study. Upon completion of the phase, study, or project, these sheets should be forwarded to HURRA, RCQ, USAMRMC.

c. ***What is Risk Level Determination?*** - HURRA has the obligation to ensure that the appropriate level of risk has been assigned to each project. In some cases, HURRA will make a different determination of risk from that of the proposed recipient's local Institutional Review Board (IRB). In those instances, HURRA will notify the PI. In the case of exempt studies, the investigator must explain in the proposal what samples will be used, how and when they were collected, and what personal identifying information will be provided to the investigator. Database studies involving the use of personal identifying information are considered minimal risk, and a consent form must be provided.

Minimal risk studies involve tests and procedures that would mirror what the subject would normally encounter during a routine test or medical examination.

Greater than minimal risk studies involve all other procedures not considered routine. All investigational new drug studies are greater than minimal risk. Selected minimal risk and all greater than minimal studies will be reviewed by The Surgeon General's Human Subjects Research Review Board.

d. ***What are the Guidelines of Waiver of Informed Consent?*** - Generally, the HURRA will not grant a waiver of informed consent for minimal risk and greater than minimal risk studies involving human beings as experimental subjects. However, minimal risk studies involving the use of **existing data** might be eligible for waiver, upon request by the investigator.

e. ***What is the HURRAD Address?*** - Should it be inconvenient to fax questions, comments, or suggestions, please feel free to write us at:

Commander
U.S. Army Medical Research and Materiel Command
Attention: MCMR-RCQ-HR
504 Scott Street
Fort Detrick, MD 21702-5012

f. ***What is a Medical Monitor?*** - A medical monitor must be assigned to research studies with human subjects involving greater than minimal risk. The name and curriculum vitae of the medical monitor must be provided. This individual should be a qualified physician, other than

the PI, who is not associated with the protocol, is able to provide medical care to research subjects for conditions that may arise during the conduct of the study, and will monitor the subjects during the conduct of the study.

4. POLICIES AND PROCEDURES:

Policies and procedures governing the use of human subjects and human anatomical substances are contained in the following documents:

- Code of Federal Regulation, Title 21 Part 50 (21 CFR 50)
- Code of Federal Regulation, Title 21 Part 56 (21 CFR 56)
- Code of Federal Regulation, Title 21 Part 312 (21 CFR 312) (when using investigational drugs/vaccines)
- Code of Federal Regulation, Title 21 Part 812 (21 CFR 812) (when using investigational devices)
- Code of Federal Regulation, Title 32 Part 219 (32 CFR 219)
- Code of Federal Regulation, Title 45 Part 46 (45 CFR 46), Subparts B, C, and D
- 10 United States Code, Section 980 (10 USC 980)
- Federal Acquisition Regulation 52.228-7 (FAR 52.228-7) (liability to third-party persons)
- Federal Acquisition Regulations 52.224-1 and 52.224-2 (privacy act information)

⇑Copies of the above can be obtained from:

U.S. Government Printing Office
North Capital & G Street, NW
Washington, DC 20401
Phone: (202)512-1800

- Department of Defense Directive 3216.2 (when using organs or tissues obtained at autopsy)
- Department of Defense Directive 6465.2
- Army Regulation 40-7 (when using investigational drugs/vaccines or schedule 1 controlled substances)
- Army Regulation 70-25

⇑Copies of these documents can be obtained from:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (703)487-4650 or 4684

(insert Optional Form 310 here)

Appendix 6
Research Involving Animals

If using animals, please complete this entire appendix. If your subcontractor is using animals, please see item #9 below.

Department of Defense (DOD) definition of **animal: Any live nonhuman vertebrate.**

Department of Defense Directive 3216.1, dated April 17, 1995, provides policy and requirements for the use of animals in DOD-funded research. **These requirements may differ from those of other funding agencies.** Each of the items listed below **must be** addressed in a proposal appendix entitled "Research Involving Animals." Questions concerning animal use should be directed to:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-AR
504 Scott Street
Fort Detrick, MD 21702-5012
Phone: (301)619-2144
Fax: (301)619-7803

1. **Literature Searches:**

   Alternatives. Identify the services (computer databases, literature searches, etc.) used to obtain information on alternatives to painful procedures. This includes alleviated pain. (The USAMRMC reserves the right to request evidence that an alternatives search was performed.)

   Duplication. Identify the databases searched to ensure that unnecessary duplication of previous experiments does not occur. (The USAMRMC reserves the right to request evidence that a duplication search was performed.)

2. **Rationale/Justification for Using Animals:** Provide a statement of the rationale/ justification for using animals. Were alternatives to animal use considered; i.e., computer modeling, cell cultures, etc.? **It is USAMRMC policy that alternatives to the use of animals be thoroughly investigated prior to submission of any proposal involving animals.**

3. **Species Identification and Rationale/Justification:** Identify the species of animals to be used and the rationale/justification for their use. Why was this particular animal model(s) chosen? Is there a unique quality or usefulness about this species that warrants its selection for use in the proposed research?

4. **Number of Animals Required and Rationale/Justification:** Provide the number of each species of animals to be used by experimental design and a scientific/mathematical rationale/ justification for how it was determined to be the minimum number required to obtain valid results.

5. **Animal Research:** Provide a complete description of the proposed use of the animals by experimental design. Include surgical procedures; biosamples (frequency, volume, harvest site, and method of tissue collection); and adjuvants and other injections (agent, dosage, route, and anatomical site of administration).

6. **Anesthesia/Analgesia/Tranquilization:** Describe what anesthetics, tranquilizers, and analgesics will be used by agent, dosage, route, and anatomical site of administration. If none are to be used, provide an explanation.

7. **Study Endpoint:** What is the projected endpoint or termination of the study for the animals?

8. **Euthanasia or Final Disposition:** Describe the method of euthanasia by agent, dosage, route, and anatomical site of administration. If animals are not euthanized, state final disposition of the animals.

9. **IACUC Approval:** Provide evidence of protocol approval from the Institutional Animal Care and Use Committee(s) (IACUC) where animal research will be performed including any subcontracting facility. If it was not possible to have the protocol reviewed by the Committee prior to submission of the proposal, then so state. Evidence of committee review can follow proposal submission, but must be provided prior to award. **RESEARCH WILL NOT BE FUNDED WITHOUT EVIDENCE OF APPROVAL FROM THE IACUC(s).**

10. **USDA Inspection Report:** Include a copy of the most recent U.S. Department of Agriculture Inspection Report (APHIS Form 7008, Inspection of Animal Facilities, Sites or Premises) for the facility(s) where the animal research will be performed.

11. **Qualifications:** Provide information on the qualifications and training of personnel performing the animal procedures. It must specifically address the training and experience these personnel possess in using and manipulating the species of animals detailed in the proposal.

12. **Accreditation:** <u>One</u> of the following must be provided for each facility where the animal research will be conducted:

    - Evidence that the facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC-I).

    - A copy of the Institutional Letter of Assurance of Compliance with the "Public Health Service Policy on Humane Care and Use of Laboratory Animals," revised September 1986.

- A statement signed by the Institutional Official that the care and use of animals will be performed according to the National Research Council 1996 "Guide for the Care and Use of Laboratory Animals" and applicable Federal regulations.

13. **Principal Investigator Signed Assurances:** The Principal Investigator must provide the following signed assurances:

    - I assure that discomfort and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research and that analgesic, anesthetic, and tranquilizing drugs will be used where indicated and appropriate to minimize discomfort and pain to animals.

    - I assure that the animals authorized for use in this protocol will be used only in the activities, manner, and quantities described herein, unless a deviation is specifically approved by my IACUC and the USAMRMC Animal Use Review Division.

    - I accept full responsibility for the proper care and use of the animals during the conduct of research outlined in the proposal.

    - I verify that I have made a reasonably good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

    - I verify that the personnel performing the animal procedures/manipulations described in this protocol are technically competent in those procedures and have received training on the use of animals in research as required by the Animal Welfare Act of 1985.

    - I assure that I have consulted with an individual who is qualified to evaluate the statistical design or strategy of this proposal and that the minimum number of animals needed for scientific validity are used.

NOTE: For proposals that require the use of nonhuman primates, companion animals, marine mammals, or protocols deemed sensitive by the USAMRMC, a site visit shall be conducted as necessary by the USAMRMC Animal Use Review Officer or designees.

Appendix 7
Safety Program Plan

Each of the items below must be addressed in a proposal appendix entitled "Safety Program Plan" and must be prepared specifically for this proposal. Each section should be operation/research specific and addressed in order. Those items that do not apply to the proposed research will be labeled as "not applicable" or "N/A." Institutional safety manuals may be referenced; however, do not send copies of safety manuals.

1. The recipient shall submit the following paragraph as affirmation that a safety program is in place and in accordance with all applicable regulations.

   (Recipient name) affirms that there is an existing safety program that is in accordance with appropriate Federal, state, and local regulations, as required by the Occupational Safety and Health Act; that hazards have been identified, eliminated, and/or controlled; and that research may be performed safely under the laboratory conditions. (Recipient name) shall be held responsible and liable for inaccuracies of the information provided, failure to implement an effective safety and occupational health program, and/or adverse conditions that may result from the failure of the recipient to identify hazard information.

2. There shall be a description of the safety procedures relating to the research operations. These should include but are not limited to the following: description of safety procedures for performing the protocol; description of any special skills, training, and standing operating procedures to assure safe research and operations (to include emergency procedures); description of medical surveillance and support; and description of security controls necessary to ensure accountability.

3. There shall be a description of the safety programs (and corresponding training) in place to include but not be limited to Hazard Communications, Chemical Hygiene, and/or Bloodborne Pathogens.

4. There shall be a description of the facility where the research will take place. This should include a description of any ventilation system employed, fire protection equipment in place, and emergency equipment available.

5. There shall be a written hazard analysis and/or tests used to identify hazards. There shall be a description of each hazard identified, a hazard analysis based on maximum credible event, and a recommendation to minimize or eliminate hazard(s).

6. There shall be a written hazard analysis of potential health hazards posed as a result of the research to be performed. These should include infectious materials, bloodborne pathogens, toxic substances, and/or ionizing and non-ionizing radiation.

7. There shall be an identification of hazardous and environmentally unacceptable materials used in the research, use of possible alternative materials, and recommended actions to eliminate or reduce the use of hazardous materials. Address any exposure concerns to personnel or the public during research and/or operations (to include transportation, packing, and shipping) or resulting from laboratory research. Special disposal procedures should be considered.

8. If radioactive materials are used, the materials and the disposal method should be identified. A copy of the NRC-approved license shall be submitted (not a copy of the organization's sub-license). If no such material is to be used, it should be so stated.

9. Any research involving recombinant DNA must meet or exceed NIH Guidelines for Research Involving Recombinant DNA Molecules, latest edition. Included should be a discussion of these requirements. A copy of the organization's institutional Biosafety Committee approval or exemption of the research shall be submitted.

10. Any other safety data that pertain to the research that may clarify the program shall be submitted.

Appendix 8
Sample Statements of Work

CEPTOR, R.E.

Statement of Work

Development of Peptide Inhibitors of the "Cancer" Receptor

Task 1. To identify the minimal region of the CR polypeptide able to inhibit intact CR when co-expressed in cultured cells (months 1-18)

- develop a series of plasmids for expressing the CR open reading frame (months 1-7)
- perform assays to ascertain which fragments of CR block DNA-binding (months 7-18)
- confirm that fragments of the CR open reading frame that block DNA-binding activity also inhibit CR function in vivo (months 18-24)

Task 2. To identify short peptides modeled after the receptor that act as inhibitors of DNA-binding and subunit association (months 18-36)

- obtain synthetic CR peptides (months 18-21)
- test the effect of synthetic peptides on the DNA-binding activity of CR (months 20-24)
- characterize the inhibitory potency of active peptides and attempt to optimize the effect by testing additional overlapping peptides (months 21-36)
- perform feasibility experiments to assess the ability of selected peptides to inhibit CR function in cultured cells (months 20-36)

Statement of Work

Follow-up Care for Men and Women with Lung Cancer

Task 1. Develop Plan for follow-up patient interviews, Months 1-3:

a. The tracking system shell from the previous lung cancer project will be modified to track patient recruitment and contact process.
b. The follow-up patient interview will be pre-screened with lung cancer patients from our hospital who are not enrolled in our study and modifications will be incorporated.
c. The environmental process interview (EPI) used for the baseline interview will be adapted for the follow-up interview.
d. Institutional Review Board approval will be obtained from all hospital sites.
e. The patient interviewer will be trained in medical terminology, measures of the interview, and use of the modified EPI system.

Task 2. Preparation for Medical Record Abstractions, Months 3-9:

a. The Medical Record Abstract form will be finalized and the investigator trained to perform patient data reviews using the instrument.
b. The Medical Record Abstract form will be revised for direct computer data entry.

Task 3. Subject Recruitment and Data collection, Months 9-20:

a. Patients enrolled in our previous study will be recruited for the proposed follow-up study.
b. Interviews subsequent to the first follow-up will be modified as necessary to reflect issues relevant to patients beyond the period of adjuvant therapy.
c. Surveys will be sent to and data collected from enrolled patients every six months.

Task 4. Abstraction of Medical Records, Months 12-24:

a. Medical record abstractions will be performed for surviving enrolled patients annually.
b. Data entry and quality control measures will be on-going.
c. Follow-up interviews will be conducted once annually with surviving enrolled patients over the 4-year study period.

Task 5. Interim Analyses, Months 24-44:

a. Interim statistical analyses of data obtained from interviews and medical record abstractions will be performed periodically.
b. Annual reports will be written.

Task 6. Final analyses and report writing, Months 44-48**:**

a. Final analyses of data from interviews and medical record abstractions will be performed.
b. A final report and initial manuscripts will be prepared.

Statement of Work

Ultrasound Imaging

Task 1. Modification of ultrasound imaging gantry, Months 1-12:

a. Modify imaging gantry to permit measurements of the optics.
b. Perform measurements using a multi-modal scanning configuration.
c. Design of final optics.

Task 2. Extensive evaluation of ultrasound imaging gantry with the final optics, Months 13-36:

a. Repeat measurements using the final optics.
b. Measure the contrast improvement provided by the new detector configuration relative to conventional detector configuration.
c. Conduct specimen experiments to evaluate the increase in resolution provided by the magnification.
d. Investigate the extent of artifacts in fixed and scanning modes.
e. Participate in design of a clinical evaluation study comparing modified ultrasound mammography with conventional mammography.